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10/730,549	12/05/2003	Mary J. Laughlin	CWRU-P01-046	1488

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EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	**PAPER NUMBER**
1651	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/730,549	LAUGHLIN ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-14,16-43,45-57 and 62-69* is/are pending in the application.

4a) Of the above claim(s) *5,9,18,22,37-39 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8,10-14,16,17,19-21,23-36,40-43,45-47,49-57 and 62-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 December 2003 and 11 August 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 3/16/07 to claims 1, 3, 8, 12, 20, 43, 45-47, 49-54, 57, 62, and 63 and withdrawn claims 5 and 48 have been entered. Claims 6, 7, 15, and 44 have been cancelled in the 3/16/07 reply. Claims 64-69 have been added. Claims 1-5, 8-14, 16-43, 45-57, and 62-69 remain pending in the current application, of which claims 1-4, 8, 10-14, 16, 17, 19-21, 23-36, 40-43, 45-47, 49-57, and 62-69 are being considered on their merits. Prior art references not included with this Office action can be found in a prior action.

Specification

The disclosure is objected to because of the following informalities: The abbreviation "EGC" for "endothelial generating cells" is misspelled ("ECG") at lines 26 and 27 of page 14 in the as-filed specification. The entire disclosure should be carefully reviewed to verify that proper acronyms are employed throughout. Appropriate correction is required.

The abstract of the disclosure is objected to because it is not of sufficient length and detail to describe the instant invention. Furthermore, the abstract is replete with legal language and phrases that can be inferred, *e.g.* "The invention provides, among other things, methods..." and "a subject in need thereof." Correction is required. See MPEP § 608.01(b) for specific guidelines for the abstract.

Drawings

The drawings are objected to because the photographs in Figures 1, 2, 6, 13, 14, 16, and 18 are dark and unintelligible. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

It is noted that applicant submitted color figures on 8/11/04, but color photographs and color drawings are not accepted unless a petition filed under 37 CFR 1.84(a)(2) is granted. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following

language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings and black and white photographs have been satisfied. See 37 CFR 1.84(b)(2).

Claim Objections

The objections to the claims are withdrawn in light of the claim amendments.

Claim Rejections - 35 USC § 112

The rejections under 35 U.S.C. § 112, second paragraph, are withdrawn in light of applicant's comments and amendments to the claims unless specifically discussed below.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 8, 10-14, 16, 16, 19-21, 23-36, 40-43, 45-47, 49-57, and 62-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising enriching $CD133^+$ or $CD133^+CD34^+$ endothelial progenitor cells from bone marrow mononuclear cells, does not reasonably provide enablement for a method comprising enriching all other types of endothelial generating cells from bone marrow mononuclear cells. Furthermore, the specification is enabling for a method of treating ischemic tissue comprising administering $CD133^+$ or $CD133^+CD34^+$ endothelial progenitor cells, but not for a method of treating ischemic

tissue comprising administering any other endothelial generating cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The specification discusses both "endothelial generating cells (EGCs)" and "endothelial progenitor cells (EPCs)." EGCs are defined at page 14, lines 26-28, of the as-filed specification as "any cell which can differentiate into an endothelial cell [including] embryonic stem cells, hemangioblasts, pluripotent stem cells, hematopoietic stem cells, and endothelial precursor cells." At least one of these species, *i.e.* embryonic stem (ES) cells, are not present in bone marrow mononuclear cells (BMC), so the specification cannot possibly provide sufficient guidance for enriching ES cells from BMC. Furthermore, information from MedScape Today (2003, reference U; retrieved from the Internet at http://www.medscape.com/viewarticle/468360_12 on 4/3/07) indicates that hepatic stem cells (the "side population") are pluripotent in that they can differentiate to liver tissue as well as to cardiomyocytes and endothelial cells

(page 1, last sentence of first paragraph). Hepatic stem cells, however, are not a component of BMC. Applicants have not enabled the enriching step for each and every embodiment encompassed by the definition of "EGCs."

EPCs, on the other hand, are one embodiment of EGCs. EPCs are described beginning at page 15, line 4, of the as-filed specification, but no limiting definition is provided for this cell population. At page 15, lines 6-7, the specification teaches that some EPCs are $CD133^+$ cells, while at lines 12-13, other EPCs are described as being $CD133^+CD34^+$. At page 27, line 20, through page 28, line 6, and page 29, lines 16-25, the specification discloses methods for enriching $CD133^+$ cells from BMC. The specification in view of the art does not provide any manner of enriching any EPCs other than $CD133^+$ EPCs.

Furthermore, the specification does not provide sufficient guidance for treating ischemia with any EGCs other than $CD133^+$ EPCs. At page 43, line 1, through page 44, line 3, the specification teaches a method for coadministering these $CD133^+$ EPCs with mesenchymal stem cells (MSCs) to a mouse hindlimb ischemia model. No evidence is provided in the specification or could be found in the art that provides an enabling disclosure for treating ischemia with MSCs and any of the EGCs listed at page 14, lines 27-28, in particular **any** pluripotent stem cell.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. Claim 8 requires expanding endothelial generating cells (EGCs) under "culture conditions that promote the formation of endothelial cells," but these conditions are not particularly pointed out in the claim for each and every species of EGC. Clarification is required.

Applicant alleges that culturing conditions are provided at "paragraph 69," which corresponds to page 18, lines 1-7, of the as-filed specification. This argument has been fully considered, but it is not persuasive. The conditions at page 18 are only applicable to bone marrow-derived EPCs (see Kalka et al., 2000, *Proceedings of the National Academy of Sciences USA* 97: 3422-3427; reference CII on 12/3/04 IDS; specifically, page 3422, column 2). The specification does not define the claimed conditions for all EGCs, for example for ES cells or for each and every pluripotent stem cell. The metes and bounds of the claim are not particularly pointed out.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 8, 10-14, 16, 17, 19-21, 23-36, 40-43, 45-47, 49-57, and 62-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strauer et al. (2002, *Circulation* 106: 1913-1918; reference CAAA on 12/3/04 IDS) taken in view of Ueno et al. (U.S. Patent Application Publication 2002/0037278), Kocher et al. (2001, *Nature Medicine* 7: 430-436; reference V), and Itescu (2003, U.S. Patent Application Publication 2003/0199464; reference AM on 12/3/04 IDS). This rejection reads on the embodiment in which the EGCs are $CD133^+$ $CD34^+$ EPCs.

Strauer et al. teach isolating bone marrow (BM) from humans (page 1914, column 1, paragraph 5); isolating bone marrow mononuclear cells (BMCs) therefrom; cultivating them overnight in a buffered tissue culture medium comprising autologous serum (page 1914, column 2, paragraph 1), and administering over 10^6 BM-MNCs to the ischemic tissue using a balloon catheter, specifically via intracoronary administration at ischemic myocardium in a subject in need thereof (page 1914, column 2, paragraph 2; page 1915, column 2, paragraph 3). Strauer et al. teach administering between $1.5x10^6$ and $4x10^6$ BM-MNCs 6 or 7 times, *i.e.*, between $9x10^6$ and $2.8x10^7$ BM-MNCs; Strauer et al. also teach that 0.65% of BM-MNCs are $AC133^+$ ($CD133^+$). Therefore, Strauer et al. teach administering between $5.9x10^4$ and $1.8x10^5$ $AC133^+$ EPCs. Strauer et al. teach that said injections resulted in improved cardiac function, cardiac geometry, and contractility (page 1915, column 2). Strauer et al. teach that their BMCs comprise mesenchymal stem cells (MSCs) as well as endothelial progenitor cells (EPCs; page 1916, column 2, paragraph 2).

Strauer et al. do not teach enriching $CD133^+$ EPCs at least two-fold prior to administration to the subject. Strauer et al. do not teach administering cells in the ratios recited in claims 28, 53, 67, and 68. Strauer et al. do not teach all of the modes of administration recited in claims 29-32. Strauer et al. do not teach coadministering the cells with VEGF or any recombinant polypeptide, as in claims 40-43. Strauer et al. do not teach administering allogeneic EPCs.

Ueno et al. teach methods for treating ischemic tissues by administering bone marrow mononuclear cells; Ueno et al. teach that the administration may be local or systemic and may be carried out via injection or infusion into arteries or veins, directly into an occlusion, or application into a tissue or organ of interest (paragraphs 0034 and 0035). Ueno et al. teach that large amounts of cells may be administered to patients safely (paragraph 0037) and that the number of cells administered is optimizable (paragraph 0034). Ueno et al. teach coadministering recombinant VEGF with the BMCs (paragraph 0042).

Kocher et al. teach that bone-marrow-derived angioblasts, which express AC133 and CD34, among other markers (page 431, column 2, last sentence), promote revascularization of infarcted myocardium (Abstract; page 432, column 2, paragraph 2; Figure 3). Kocher et al. teach that angioblasts isolated to 98% purity express AC133 (page 435, column 1, paragraph 4). Kocher et al. teach that administration of their $CD34^+$ $AC133^+$ cells may be combined with other therapies (Abstract; page 435, column 1, paragraph 3).

Itescu teaches methods for regenerating myocardial tissue after ischemic damage by promoting neovascularization with an injection of endothelial progenitor cells (paragraph 0055). The EPCs of Itescu are found in bone marrow (paragraph 0056), express CD34 and CD133 (paragraph 0061), and may be allogeneic with respect to the recipient (paragraph 0057). Itescu teaches that the number of cells administered to the patient may vary (paragraph 0056), as may the location of the injection (paragraph 0061).

A person of ordinary skill in the art would have had a reasonable expectation of success in enriching the $CD133^+$ EPCs within the BM-MNCs of Strauer et al. at least twofold because Kocher et al. teach methods for enriching such cells to 98% purity. The skilled artisan would have been motivated to enrich the $CD133^+$ EPCs in the administered composition of Strauer et al. because Kocher et al. recognized that $CD133^+$ cells promote neovascularization of ischemic tissue; therefore, administering more cells known at the time of the invention to achieve the desired result of Strauer et al. would improve the outcome of the method of Strauer et al.

The person of ordinary skill in the art would have had a further reasonable expectation of success in coadministering the VEGF of Ueno et al. with the cells of Strauer et al. in the method of Strauer et al. because Ueno et al. teach methods for administering recombinant polypeptides and that such polypeptides may be coadministered with cells. The skilled artisan would have been motivated to include VEGF with the stem cells in the method of Strauer et al. because Ueno et al. teach that

VEGF is a growth factor that promotes neovascularization upon administration to a patient.

The person of ordinary skill in the art would have had a further reasonable expectation of success in administering allogeneic cells in the method of Strauer et al. because Itescu teaches that allogeneic EPCs promote neovascularization. The skilled artisan would have been motivated to administer allogeneic EPCs in the method of Strauer et al. for the expected benefit that the pool of donor cells would be dramatically increased in size.

The selection of the mode of administration of the cells in the method of Strauer et al. would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Ueno et al. and Itescu both teach that ischemia may be treated bone marrow-derived cells administered in any of a variety of means. A holding of obviousness over the cited claims is therefore clearly required.

The selection of the number of each type of cell to administer in the method of Strauer et al. would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Strauer et al., Ueno et al., and Itescu all teach that these numbers may be modified depending on the desired outcome. A holding of obviousness over the cited claims is therefore clearly required.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to enrich the $CD133^+$ EPCs from the BM-MNCs of Strauer et al. using the methods of Kocher et al. and administer more such $CD133^+$ EPCs with the mesenchymal stem cells in the method of Strauer et al. because Kocher et al. teach

that $CD133^+$ EPCs promote neovascularization. It would have been further obvious to coadminister recombinant VEGF with the cells in the method of Strauer et al. because Ueno et al. teach that VEGF is a growth factor that promotes neovascularization and aids in treating ischemia. It would have been further obvious to administer allogeneic EPCs in the method of Strauer et al. because Itescu teaches that allogeneic EPCs promote neovascularization. Finally, it would have been further obvious to vary the numbers of each type of cell administered and the mode of administration because Strauer et al., Ueno et al., and Itescu concur that these are optimizable variables for the reasons discussed above.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant's arguments regarding the withdrawn art rejections have been considered to the extent they read on this new ground of rejection. Regarding the rejection under 35 U.S.C. § 102 over Ueno et al., Applicant alleges that Ueno et al. do not teach enrichment of any population (Reply, page 13, paragraph 1). Applicant alleges that Ueno et al. do not teach the numbers and ratios of cells recited in the instant claims (Reply, page 13, paragraphs 3 and 4). Applicant alleges that Ueno et al. do not teach intracoronary administration (Reply, page 13, paragraph 5) or culturing any cells prior to administration (Reply, page 13, paragraph 6). Applicant supplies similar arguments against the rejections under 35 U.S.C. § 102 over Tatesishi-Yuyama et al. (Reply, page 14, paragraph 5 *et seq.*) and Strauer et al. (Reply, page 16, paragraphs 1-4) and under

35 U.S.C. § 103 over Ueno et al. (page 17), Kalka (page 18), and Kawamoto (page 19). These arguments have been fully considered, but they are not persuasive.

The claims examined for the first Office action in this application did not require that the EGCs be enriched at least two-fold from BMCs, but rather that EGCs be enriched two-fold relative to some unnamed standard. The requirement that EGCs be enriched relative to BMCs is a new limitation and the reason for the new ground of rejection. While Ueno et al. and Strauer et al. do not teach enriching these cells from BMCs, Kocher et al. do teach such a method and the motivation for doing so. When the three references are considered together, the enrichment from BMCs is rendered obvious.

The examiner does not agree that Ueno et al. do not teach the exact numbers of cells; in any case, both Ueno et al. and Strauer et al. teach that the numbers of cells administered to patients is optimizable. In the absence of evidence of criticality of the claimed ratios and quantities, these limitations would have been obvious variants and well within the bounds of routine experimentation for the skilled artisan at the time of the invention.

As to intracoronary administration and the culturing steps, this rejection is over Strauer et al., which teaches both of these limitations, taken in view of other references. When the three references are considered together, the culturing step and intracoronary administration are both rendered obvious.

No claims are allowed. No claims are free of the art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Lora E Barnhart

leb

SANDRA E. SAUCIER
PRIMARY EXAMINER